PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 28 July 2000 (28.07.00)	
International application No. PCT/EP99/10084	**Applicant's or agent's file reference** C 2681 PCT
International filing date (day/month/year) 17 December 1999 (17.12.99)	**Priority date** (day/month/year) 17 December 1998 (17.12.98)
Applicant DE VEYLDER, Lieven et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

18 May 2000 (18.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Zakaria EL KHODARY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

NSA

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Articl 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
C 2681 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/ 10084	17/12/1999	17/12/1998
Applicant		
CROPDESIGN N.V. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [X] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

PLANT CELL CYCLE GENES AND USES THEREOF

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

[ ] as suggested by the applicant.

[X] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/10084

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 37 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 34
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1,5-38,40 (inventions 1 and 4)

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 34

Claim 34 and in part claim 35 and 36 refer to an activator/inhibitor of cell division without giving a true technical characterization. Moreover, no such compounds are defined in the application. In consequence, the scope of said claims is ambigous and vague, and their subject-matter is not sufficiently disclosed and supported (Art. 5 anf 6 PCT).
No search can be carried out for such purely speculative claims whose wording is, in fact, a mere recitation of the result to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,5-38,40 partially

DNA sequence encoding the cell cycle interacting protein LDV115 as characterized by SEQIDs 1 + 2, respectively; furthermore a method for identifying cell cycle interacting proteins by using a two-hybrid system with CDC2a or CDC2b as bait; the recombinant expression of the same in host cells; generation of an antibody to said proteins; furthermore a method for generating transgenic plants that exhibit reduced synthesis of said cell cycle interacting proteins; furthermore the identification of the corresponding promoter sequences of said proteins; a method for the identification of activators or inhibitors of said proteins and cell division in general by establishing a read-out system interacting with either the promoter region or the protein and operating the read-out system in the presence of a compound; a method for producing a therapeutic or plant effective agent containing said activator or inhibitor; a composition containing said genes, proteins, vectors, antibodies or activators or inhibitors for use as a medicament or plant effective agent; use of the nucleotide sequences representing said proteins or promoters in marker-assisted breeding;

2. Claims: 1,5-38,40 partially; 41-45 completely

as invention 1 but limited to the PHO80-like proteins as characterized by SEQIDs 3,4,33,34,35,36,37,38,39,40,41,42; and furthermore a method for improving tolerance of plants towards phosphate by modulating the expression of said PHO80-like proteins, the use of said proteins as selectable markers in transformation.

3. Claims: 1,5-38,40 partially

as invention 1 but limited to the VB33 protein as characterized by SEQIDs 5 + 6.

4. Claims: 1,5-38,40 partially

as invention 1 but limited to the VB89 protein as characterized by SEQIDs 7 + 8.

5. Claims: 1,5-38,40 partially

as invention 1 but limited to the VBDAHP protein as characterized by SEQIDs 9 + 10.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

6. Claims: 1,5-38,40 partially

as invention 1 but limited to the VBDBP protein as characterized by SEQIDs 11 + 12.

7. Claims: 1,5-38,40 partially

as invention 1 but limited to the VBHSF protein as characterized by SEQIDs 13 + 14.

8. Claims: 2,3,4,39 completely; 5-38,40 partially

Method for identifying cell cycle interacting proteins or activators or inhibitors of such proteins by using a two-hybrid screening assay utilizing CDC2a or CDC2b proteins as bait and a plant cell suspension library as prey.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/10084

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/82 C07K14/415 C12Q1/68 G01N33/50 C12N1/20
C07K16/16 A01H5/00 C12N15/11 A61K38/16 A61K39/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K C12N G01N A61K A01H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, MEDLINE, STRAND, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CULIANEZ-MACIA, F.A., ET AL. : "Arabidopsis HAL3A: identification of a novel flavoprotein which regulates plant growth and salt tolerance - unpublished" EMBL SEQUENCE DATA LIBRARY, 19 January 1997 (1997-01-19), XP002144143 heidelberg, germany accession no.U80192; AF166263; Y09716 ---	1,5,11, 37
A	CULIANA-MACIA, F.A:, ET AL. : "Arabidopsis thaliana HAL3 homolog gene" SWISSPROT DATABASE, 1 May 1997 (1997-05-01), XP002144144 accession no. P94063 --- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 August 2000	13.09.00
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Holtorf, S

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DE VEYLDER LIEVEN ET AL: "The Arabidopsis CKs1At protein binds the cyclin-dependent kinases Cdc2aAT and Cdc2bAt." FEBS LETTERS 1997, vol. 412, no. 3, 1997, pages 446-452, XP002047992 ISSN: 0014-5793 see especially page 449, right column; page 450; Figs. 1 + 6; Materials and Methods on page 446 the whole document ---	1,5-38, 40
A	DE NADAL EULALIA ET AL: "The yeast halotolerance determinant Hal3p is an inhibitory subunit of the Ppz1p Ser/Thr protein phosphatase." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 95, no. 13, 23 June 1998 (1998-06-23), pages 7357-7362, XP002144145 June 23, 1998 ISSN: 0027-8424 the whole document ---	
A	DE VEYLDER L ET AL: "Identification of proteins interacting with the Arabidopsis Cdc2aAt protein." JOURNAL OF EXPERIMENTAL BOTANY DEC., 1997, vol. 48, no. 317, December 1997 (1997-12), pages 2113-2114, XP002067456 ISSN: 0022-0957 the whole document ---	1,5-38, 40
A	WO 98 41642 A (VEYLDER LIEVEN DE ;VLAAMS INTERUNIV INST BIOTECH (BE); INZE DIRK () 24 September 1998 (1998-09-24) the whole document ---	1,5-38, 40
A	WANG H. ET AL.: "ICK1, a cyclin-dependent protein kinase inhibitor from Arabidopsis thaliana interacts with both Cdc2a and CycD3, and its expression is duced by abscisic acid." PLANT J 1998 AUG;15(4):501-10, XP002054969 the whole document --- -/--	1,5-38, 40

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	SEGERS GERDA ET AL: "The Arabidopsis cyclin-dependent kinase gene cdc2bAt is preferentially expressed during S and G-2 phases of the cell cycle." PLANT JOURNAL 1996, vol. 10, no. 4, 1996, pages 601-612, XP002138663 ISSN: 0960-7412 ---	
A	WO 98 03631 A (SALK INST FOR BIOLOGICAL STUDI) 29 January 1998 (1998-01-29) the whole document ---	1,5-38, 40
P,X	CHEN, J., ET AL. : "arabidopsis thaliana gene expression microarray - unpublished" EMBL SEQUENCE DATA LIBRARY, 9 September 1999 (1999-09-09), XP002144147 heidelberg, germany accession no. AW004542 ---	1,5
T	ESPINOSA-RUIZ, A., ETAL. : "Arabidopsis thaliana AtHAL3: a flavoprotein related to salt and osmotic tolerance and plant growth" THE PLANT JOURNAL , vol. 20, no. 5, December 1999 (1999-12), pages 529-539, XP002144146 the whole document -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/10084

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9841642 A	24-09-1998	AU 6730198 A	12-10-1998
		EP 0972060 A	19-01-2000
WO 9803631 A	29-01-1998	AU 3960597 A	10-02-1998
		BR 9710872 A	17-08-1999
		CA 2260287 A	29-01-1998
		EP 0929663 A	21-07-1999

10/31

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
C 2681 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/10084	17/12/1999	17/12/1998
International Patent Classification (IPC) or national classification and IPC C12N15/82		
Applicant CROPDESIGN N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/05/2000	07.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Heimann-Pohl, B Telephone No. +49 89 2399 8713

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/10084

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-102 as originally filed

Claims, No.:

1-45 as originally filed

Drawings, sheets:

1/1 as originally filed

Sequence listing part of the description, pages:

1-37, filed with the letter of 29.09.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 34 (complete), 35-37 (partially).

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 34 (complete), 35-37 (partially).

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1, 5-38, 40.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	12-33, 37-38
	No:	Claims	1, 5-11, 35-36
Inventive step (IS)	Yes:	Claims	

	No:	Claims	1, 5-33, 35-38, 40
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	1, 5-33, 35-38, 40

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1). The present application relates to plant cell cycle interacting molecules. Nucleotide sequences encoding proteins that interact cyclin- dependent protein kinases from Arabidopsis thaliania, CDC2a and CDC2b, were isolated using a two-hybrid screening. CDK-cyclin complexes are known in animal systems and yeast. Plants contain a unique class of CDK, e.g. CDC2b, in Arabidopsis thaliana, which structurally and functionally differ from animal and yeast CDK.

2). Unity (Box IV)

Due to the fact that nucleotide sequences encoding proteins that interact with cyclin- dependent protein kinases from Arabidopsis thaliania using a two-hybrid screen has already been disclosed in the prior art (WO 98 41642 a (VEYLDER LIEVEN DE ;VLAAMS INTERUNIV INST BIOTECH (D6), DE VEYLDER LIEVEN ET AL, FEBS LETTERS 1997, vol. 412, no. 3, 1997, pages 446-452 (D3), DE VEYLDER L ET AL, JOURNAL OF EXPERIMENTAL BOTANY DEC., 1997, vol. 48, no. 317, December 1997 (1997-12), pages 2113-2114 (D5)) a non-unity objection was raised by the ISA and IPEA.

The applicant has elected inventions 1 and 4 for search and examination and paid an additional fee.

Invention 1: Claims 1,5-38,40 partially

DNA sequence encoding the cell cycle interacting protein LDV115 as characterized by SEQIDs 1 and 2, respectively; a method for identifying cell cycle interacting proteins using a two-hybrid system CDC2a or CDC2b as bait; recombinant expression of the same in host cells; generation of an antibody to said proteins; a method for generating transgenic plants that exhibit reduced synthesis of said cell cycle interacting proteins; identification of corresponding promoter sequences of said proteins; method for identification of activators or inhibitors of said proteins and cell division in general by establishing a read-out system interacting with either the promoter region or the protein and operating the read-out system in the presence of a compound; method of producing a therapeutic or plant effective agent containing said activator or inhibitor; a

composition containing said genes, proteins, vectors, antibodies or activators or inhibitors for use as a medicament or plant effective agent; use of the nucleotide sequences representing said proteins or promoters in marker-assisted breeding.

Invention 4: Claims 1,5-38,40 partially

As invention 1 but limited to the VB89 protein as characterized in SEQIDs 7 and 8.

3). No Search (Box III)

Claim 34 was found to be unsearchable. Claims 35-37 embrace i.a. the unknown and unsearchable activator or inhibitor of claim 34. Consequently, this claim and claims 35-37 as far as related to subject matter of claim 34 cannot be examined. Examination is thus restricted to claims 1, 5-33, 38 and 40 and claims 35-37 partially.

4). Prior Art

D1: CULIANEZ-MACIA, F.A., ET AL. : 'Arabidopsis HAL3A: identification of a novel flavoprotein which regulates plant growth and salt tolerance - unpublished' EMBL SEQUENCE DATA LIBRARY, 19 January 1997 (1997- 01-19), XP002144143 heidelberg, germany
D2: CULIANA-MACIA, F.A:, ET AL. : 'Arabidopsis thaliana HAL3 homolog gene' SWISSPROT DATABASE, 1 May 1997 (1997-05-01), XP002144144
D3: DE VEYLDER LIEVEN ET AL: 'The Arabidopsis CKs1At protein binds the cyclin-dependent kinases Cdc2aAT and Cdc2bAt.' FEBS LETTERS 1997, vol. 412, no. 3, 1997, pages 446-452, XP002047992 ISSN: 0014-5793
D4: DE NADAL EULALIA ET AL: 'The yeast halotolerance determinant Hal3p is an inhibitory subunit of the Ppz1p Ser/Thr protein phosphatase.' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 95, no. 13, 23 June 1998 (1998-06-23), pages 7357- 7362, XP002144145 June 23, 1998 ISSN: 0027-8424
D5: DE VEYLDER L ET AL: 'Identification of proteins interacting with the Arabidopsis Cdc2aAt protein.' JOURNAL OF EXPERIMENTAL BOTANY DEC.,

1997, vol. 48, no. 317, December 1997 (1997-12), pages 2113-2114, XP002067456 ISSN: 0022-0957
D6: WO 98 41642 a (VEYLDER LIEVEN DE ;VLAAMS INTERUNIV INST BIOTECH (BE); INZE DIRK () 24 September 1998 (1998-09-24)
D7: WO-a-9841642
D8: WANG H. ET AL.: 'ICK1, a cyclin-dependent protein kinase inhibitor from Arabidopsis thaliana interacts with both Cdc2a and CycD3, and its expression is duced by abscisic acid.' PLANT J 1998 AUG;15(4):501-10, XP002054969
D9: SEGERS GERDA ET AL: 'The Arabidopsis cyclin-dependent kinase gene cdc2bAt is preferentially expressed during S and G-2 phases of the cell cycle.' PLANT JOURNAL 1996, vol. 10, no. 4, 1996, pages 601-612, XP002138663 ISSN: 0960-7412
D10: WO 98 03631 a (SALK INST FOR BIOLOGICAL STUDI) 29 January 1998 (1998-01-29)
D11: WO-a-9803631
D12: CHEN, J., ET AL. : 'arabidopsis thaliana gene expression microarray - unpublished' EMBL SEQUENCE DATA LIBRARY, 9 September 1999 (1999-09-09), XP002144147 heidelberg, germany
D13: ESPINOSA-RUIZ, a., ETAL. : 'Arabidopsis thaliana AtHAL3: a flavoprotein related to salt and osmotic tolerance and plant growth' THE PLANT JOURNAL , vol. 20, no. 5, December 1999 (1999-12), pages 529-539, XP002144146

5). Priority (Box II)

If the priority is not valid, which could not be checked, D12 will become relevant.

6). Novelty, Inventive Step and Industrial Applicability (Box V)

6.1). Novelty (Art. 33 (2) PCT)

Invention 1

The sequence for LDV115, SEQ ID NO: 1 and 2 appears to be novel with regard

to the cited prior art.

Invention 4

Claim 1 relates to a DNA sequence encoding a cell cycle interacting protein or encoding an immunologically active fragment of such a protein. D1 discloses a shorter sequence of HAL3. The description of the present application states on page 72 "Except that VB89 is longer, there are no major differences with this cDNA"
Thus the subject matter of claim 1(d) lacks novelty (Art. 33 (2) PCT).
Also the follow-up claims to the vector and the host cell of claims 5-11 as well as a composition comprising the DNA sequence of claims 35 and 36 lack novelty over D1 (or inventive step claims 12-33, 35-38 and 40 see below).

Invention 1 and invention 4

Moreover claim 1 does not require that the DNA sequence must be **isolated** consequently claim 1 as presently worded embraces sequences in their natural environment.

6.2). Inventive Step (Art. 33 (3) PCT)

Invention 1 and 4

The use of yeast two-hybrid system to identify Arabidopsis thaliana proteins interacting with CDC2aAt or CDC2bAt is known from D3, D5-D7.
Thus the problem to be solved by the present application is the identification of further plant specific cell cycle interacting proteins.

Invention 1

With regard to the LDV115 gene the description teaches (page 102) that said gene encodes a protein which interacts with CDC2a but not with DCD2b and it shows a limited similarity to the S. cerevisiae WEB1 protein. Screening publicly available databases revealed the WEB1 protein from S. pombe as best

homologue due to the proline-richness of LDV115. However, proline-rich regions are not restricted to the WEB1 protein but can also be found in many structural proteins. Therefore it is concluded in the description that "LDV115 might not be a true homologue of WEB1."
Having regard to the description apparently no physiological function or activity was determined or confirmed for LDV115 in the present application. (The ability to interact with CDC2a cannot be taken as the physiological function in view of other proteins interacting with CDC2aAt (D5).)
Thus since no proven or probable physiological function is demonstrated in the present application the only technical problem underlying the present application that could be identified by the IPEA merely resides in the cloning of new sequences and provision of the proteins with no determined/confirmed function or specific and substantial utility.
This is a "minimalist" problem which is not technically meaningful. The solution is a non-inventive selection from a host of polypeptides.
Consequently, claims 1, 5-33, 35-38 and 40 of invention 1 do not meet the requirements of Art. 33 (3) PCT.

Invention 4

With regard to D1 which is considered the closest prior art document and in combination with either D3, D5-D6 or D7 the subject matter of claims 12-33, 35-38 and 40 lack an inventive step (Art. 33 (3) PCT).

6.3). Industrial Applicability (Art. 33 (4) PCT)

Invention 1

The above analysis of the description and arguments are also of importance when considering the industrial applicability.

No physiological function or activity has been determined for LDV115.
Thus the DNA sequence and the polypeptide (LDV115) encoded by said sequence can be used to assess the properties or functions of said protein and thus serve as a starting point for further research.

Art. 33(4) PCT requires that the invention can be **mad or used** in order to have industrial applicability. According to Rule 5(vi) PCT the description must indicate explicitly, when it is not obvious from the description or nature of the invention, the way in which the invention is capable of exploitation in industry and the way in which it can be made or used.
Also the PCT International Preliminary Examination Guidelines, Chapter IV-4. (WIPO 1998) state that "a claimed invention shall be considered industrially applicable, if according to its nature, it can be made or used (in the technological sense) in any kind of industry".

Which impact have these requirements on nucleic acid molecules and polypeptides?
No doubt the nucleic acid molecules and polypeptides can be **made**.

Is this sufficient to have industrial applicability?
Making nucleic acid molecules and polypeptides without any purpose is technically and industrially not meaningful (like copying information).

Thus for chemical compounds such as nucleic acid molecules and polypeptides the **use** requirement of Art. 33(4) and Rule 5(vi) PCT must be fulfilled. This means that there must be a function/biological/physiological activity attributed to said specific nucleic acid molecule or polypeptide, which shows its industrial applicability or at least makes it plausible.
The mere finding that this protein interacts (how?) with CDC2aAt is generally not sufficient in view of the cited prior art.
It follows that in the present case the skilled person has to carry out research programme in order to find out how the DNA sequence or protein can be used in industry other than for research purposes.
Hence, with regard to the above, the subject matter of claims 1, 5-33, 35-38 and 40 does not meet the requirement of Art. 33(4)and Rule 5 (vi) PCT.
In view of the lack of determined biological activity/function of the polypeptides and in view of the speculative uses the industrial applicability does not appear to be plausible.

Invention 4

With regard to the function (role) of HAL3 of yeast and with regard to the sequence identity, it appears plausible that VB89 is a homologue to yeast HAL3.

7). Concluding remark with regard to invention 1

All that the invention 1 provides is a starting point for an invitation to carry out a research programme for the next years. This cannot be called a complete invention.

8). Clarity (Art. 6 PCT) (Box VIII)

Claim 1 does not specify that the identity must be over the entire length which renders the claim speculative.

Since the function of the protein at least for invention 1 was not determined it is not clear for which function the skilled person should look (test) when testing all the proteins or parts thereof which have 60% identity. Consequently, claim 1 is unclear.

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PCT

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C12N 15/82, C07K 14/415, C12Q 1/68, G01N 33/50, C12N 1/20, C07K 16/16, A01H 5/00, C12N 15/11, A61K 38/16, 39/00

A3

(11) International Publication Number: WO 00/36124

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98124062.5 17 December 1998 (17.12.98) EP

(71) Applicant *(for all designated States except US)*: CROPDESIGN N.V. [BE/BE]; Technologiepark 3, B–9052 Gent (BE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: DE VEYLDER, Lieven [BE/BE]; Josef Boddaertstraat 23, B–9031 Drongen (BE). BOUDOLF, Veronique, Katelijne, Cecile, Kristien [BE/BE]; Koningin Fabiolalaan 70, B–9000 Gent (BE). TORRES ACOSTA, Juan Antonio [MX/BE]; Kortrijksepoortstraat 303, B–9000 Gent (BE). INZÉ, Dirk [BE/BE]; Driesstraat 18, B–9310 Moorsel–Aalst (BE).

(74) Agent: VOSSIUS & PARTNER; P.O. Box 86 07 67, D–81634 München (DE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

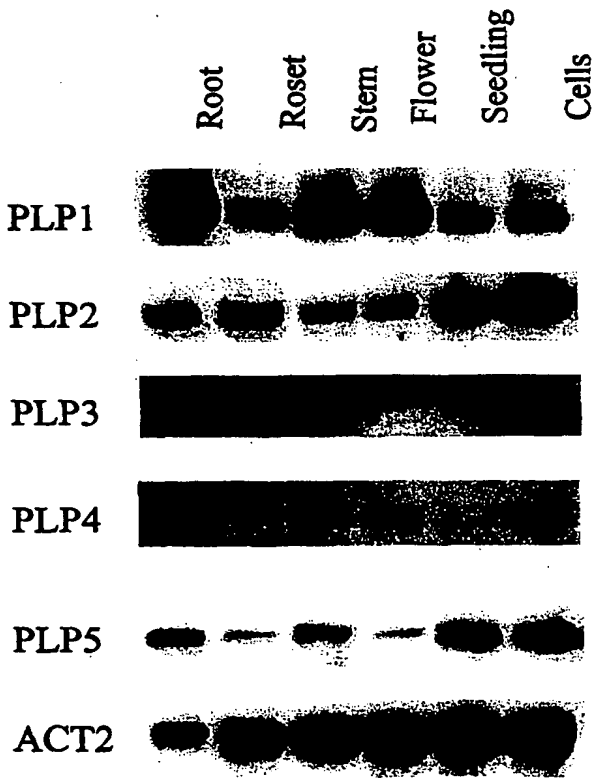
Published
With international search report.

(88) Date of publication of the international search report:
23 November 2000 (23.11.00)

(54) Title: PLANT CELL CYCLE GENES AND USES THEREOF

(57) Abstract

Provided are DNA sequences encoding cell cycle interacting proteins as well as methods for obtaining the same. Furthermore, vectors comprising said DNA sequences are described, wherein the DNA sequences preferably are operatively linked to regulatory elements allowing expression in prokaryotic and/or eukaryotic host cells. In addition, proteins encoded by said DNA sequences, antibodies to said proteins and methods for their production are provided. Also described is a method for controlling or altering growth characteristics of a plant and/or a plant cell comprising introduction and/or expression of one or more cell cycle regulatory proteins functional in a plant or parts thereof and/or one or more DNA sequences encoding such proteins. Also provided are regulatory sequences controling the expression of the above described cell cycle interacting proteins. Method for the identification of compounds being capable of activating or inhibiting the cell cycle are described as well. Furhter described are diagnostic compositions comprising the aforementioned DNA sequences, regulatory sequences, proteins, antibodies, inhibitors and activators. Furthermore, transgenic plant cells, plant tissue and plants containing the above–described DNA sequences and vectors are described as well as the use of the aforementioned DNA sequences, vectors, proteins, regulatory sequences, antibodies and/or compounds identified by the method of the invention in plant cell and tissue culture, plant breeding and/or agriculture.



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INTERNATIONAL SEARCH REPORT

Interna[redacted] Application No
PCT/EP 99/10084

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/82 C07K14/415 C12Q1/68 G01N33/50 C12N1/20
C07K16/16 A01H5/00 C12N15/11 A61K38/16 A61K39/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K C12N G01N A61K A01H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS, MEDLINE, STRAND, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CULIANEZ-MACIA, F.A., ET AL. : "Arabidopsis HAL3A: identification of a novel flavoprotein which regulates plant growth and salt tolerance - unpublished" EMBL.SEQUENCE DATA LIBRARY, 19 January 1997 (1997-01-19), XP002144143 heidelberg, germany accession no.U80192; AF166263; Y09716 ---	1,5,11, 37
A	CULIANA-MACIA, F.A:, ET AL. : "Arabidopsis thaliana HAL3 homolog gene" SWISSPROT DATABASE, 1 May 1997 (1997-05-01), XP002144144 accession no. P94063 --- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
21 August 2000	13.09.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Holtorf, S

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	DE VEYLDER LIEVEN ET AL: "The Arabidopsis CKs1At protein binds the cyclin-dependent kinases Cdc2aAT and Cdc2bAt." FEBS LETTERS 1997, vol. 412, no. 3, 1997, pages 446-452, XP002047992 ISSN: 0014-5793 see especially page 449, right column; page 450; Figs. 1 + 6; Materials and Methods on page 446 the whole document	1,5-38, 40
A	DE NADAL EULALIA ET AL: "The yeast halotolerance determinant Hal3p is an inhibitory subunit of the Ppz1p Ser/Thr protein phosphatase." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 95, no. 13, 23 June 1998 (1998-06-23), pages 7357-7362, XP002144145 June 23, 1998 ISSN: 0027-8424 the whole document	
A	DE VEYLDER L ET AL: "Identification of proteins interacting with the Arabidopsis Cdc2aAt protein." JOURNAL OF EXPERIMENTAL BOTANY DEC., 1997, vol. 48, no. 317, December 1997 (1997-12), pages 2113-2114, XP002067456 ISSN: 0022-0957 the whole document	1,5-38, 40
A	WO 98 41642 A (VEYLDER LIEVEN DE ;VLAAMS INTERUNIV INST BIOTECH (BE); INZE DIRK () 24 September 1998 (1998-09-24) the whole document	1,5-38, 40
A	WANG H. ET AL.: "ICK1, a cyclin-dependent protein kinase inhibitor from Arabidopsis thaliana interacts with both Cdc2a and CycD3, and its expression is duced by abscisic acid." PLANT J 1998 AUG;15(4):501-10, XP002054969 the whole document	1,5-38, 40

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SEGERS GERDA ET AL: "The Arabidopsis cyclin-dependent kinase gene cdc2bAt is preferentially expressed during S and G-2 phases of the cell cycle." PLANT JOURNAL 1996, vol. 10, no. 4, 1996, pages 601-612, XP002138663 ISSN: 0960-7412 ---	
A	WO 98 03631 A (SALK INST FOR BIOLOGICAL STUDI) 29 January 1998 (1998-01-29) the whole document ---	1,5-38, 40
P,X	CHEN, J., ET AL. : "arabidopsis thaliana gene expression microarray - unpublished" EMBL SEQUENCE DATA LIBRARY, 9 September 1999 (1999-09-09), XP002144147 heidelberg, germany accession no. AW004542 ---	1,5
T	ESPINOSA-RUIZ, A., ETAL. : "Arabidopsis thaliana AtHAL3: a flavoprotein related to salt and osmotic tolerance and plant growth" THE PLANT JOURNAL , vol. 20, no. 5, December 1999 (1999-12), pages 529-539, XP002144146 the whole document -----	

INTERNATIONAL SEARCH REPORT

Int. ional application No.
PCT/EP 99/10084

B x I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 37 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 34
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1,5-38,40 (inventions 1 and 4)

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 34

Claim 34 and in part claim 35 and 36 refer to an activator/inhibitor of cell division without giving a true technical characterization. Moreover, no such compounds are defined in the application. In consequence, the scope of said claims is ambigous and vague, and their subject-matter is not sufficiently disclosed and supported (Art. 5 anf 6 PCT).
No search can be carried out for such purely speculative claims whose wording is, in fact, a mere recitation of the result to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,5-38,40 partially

DNA sequence encoding the cell cycle interacting protein LDV115 as characterized by SEQIDs 1 + 2, respectively; furthermore a method for identifying cell cycle interacting proteins by using a two-hybrid system with CDC2a or CDC2b as bait; the recombinant expression of the same in host cells; generation of an antibody to said proteins; furthermore a method for generating transgenic plants that exhibit reduced synthesis of said cell cycle interacting proteins; furthermore the identification of the corresponding promoter sequences of said proteins; a method for the identification of activators or inhibitors of said proteins and cell division in general by establishing a read-out system interacting with either the promoter region or the protein and operating the read-out system in the presence of a compound; a method for producing a therapeutic or plant effective agent containing said activator or inhibitor; a composition containing said genes, proteins, vectors, antibodies or activators or inhibitors for use as a medicament or plant effective agent; use of the nucleotide sequences representing said proteins or promoters in marker-assisted breeding;

2. Claims: 1,5-38,40 partially; 41-45 completely

as invention 1 but limited to the PHO80-like proteins as characterized by SEQIDs 3,4,33,34,35,36,37,38,39,40,41,42; and furthermore a method for improving tolerance of plants towards phosphate by modulating the expression of said PHO80-like proteins, the use of said proteins as selectable markers in transformation.

3. Claims: 1,5-38,40 partially

as invention 1 but limited to the VB33 protein as characterized by SEQIDs 5 + 6.

4. Claims: 1,5-38,40 partially

as invention 1 but limited to the VB89 protein as characterized by SEQIDs 7 + 8.

5. Claims: 1,5-38,40 partially

as invention 1 but limited to the VBDAHP protein as characterized by SEQIDs 9 + 10.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

6. Claims: 1,5-38,40 partially

as invention 1 but limited to the VBDBP protein as characterized by SEQIDs 11 + 12.

7. Claims: 1,5-38,40 partially

as invention 1 but limited to the VBHSF protein as characterized by SEQIDs 13 + 14.

8. Claims: 2,3,4,39 completely; 5-38,40 partially

Method for identifying cell cycle interacting proteins or activators or inhibitors of such proteins by using a two-hybrid screening assay utilizing CDC2a or CDC2b proteins as bait and a plant cell suspension library as prey.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/10084

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9841642 A	24-09-1998	AU 6730198 A	12-10-1998
		EP 0972060 A	19-01-2000
WO 9803631 A	29-01-1998	AU 3960597 A	10-02-1998
		BR 9710872 A	17-08-1999
		CA 2260287 A	29-01-1998
		EP 0929663 A	21-07-1999

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

VOSSIUS & PARTNER
Siebertstrasse 4
81675 München
ALLEMAGNE

EINGEGANGEN
Vossius & Partner
08. März 2001
Frist
bearb.:

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 07.03.2001
Applicant's or agent's file reference C 2681 PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/10084	17/12/1999	17/12/1998

Applicant
CROPDESIGN N.V. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Guerin, A Tel.+49 89 2399-8061

Form PCT/IPEA/416 (July 1992)

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
C 2681 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/10084	17/12/1999	17/12/1998
International Patent Classification (IPC) or national classification and IPC C12N15/82		
Applicant CROPDESIGN N.V. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 12 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18/05/2000	07.03.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Heimann-Pohl, B Telephone No. +49 89 2399 8713

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/10084

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-102 as originally filed

Claims, No.:

1-45 as originally filed

Drawings, sheets:

1/1 as originally filed

Sequence listing part of the description, pages:

1-37, filed with the letter of 29.09.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 34 (complete), 35-37 (partially).

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 34 (complete), 35-37 (partially).

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☒ not complied with for the following reasons:
see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1, 5-38, 40.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 12-33, 37-38
	No:	Claims 1, 5-11, 35-36
Inventive step (IS)	Yes:	Claims

	No:	Claims	1, 5-33, 35-38, 40
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	1, 5-33, 35-38, 40

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1). The present application relates to plant cell cycle interacting molecules. Nucleotide sequences encoding proteins that interact cyclin- dependent protein kinases from Arabidopsis thaliania, CDC2a and CDC2b, were isolated using a two-hybrid screening. CDK-cyclin complexes are known in animal systems and yeast. Plants contain a unique class of CDK, e.g. CDC2b, in Arabidopsis thaliana, which structurally and functionally differ from animal and yeast CDK.

2). Unity (Box IV)

Due to the fact that nucleotide sequences encoding proteins that interact with cyclin- dependent protein kinases from Arabidopsis thaliania using a two-hybrid screen has already been disclosed in the prior art (WO 98 41642 a (VEYLDER LIEVEN DE ;VLAAMS INTERUNIV INST BIOTECH (D6), DE VEYLDER LIEVEN ET AL, FEBS LETTERS 1997, vol. 412, no. 3, 1997, pages 446-452 (D3), DE VEYLDER L ET AL, JOURNAL OF EXPERIMENTAL BOTANY DEC., 1997, vol. 48, no. 317, December 1997 (1997-12), pages 2113-2114 (D5)) a non-unity objection was raised by the ISA and IPEA.

The applicant has elected inventions 1 and 4 for search and examination and paid an additional fee.

Invention 1: Claims 1,5-38,40 partially

DNA sequence encoding the cell cycle interacting protein LDV115 as characterized by SEQIDs 1 and 2, respectively; a method for identifying cell cycle interacting proteins using a two-hybrid system CDC2a or CDC2b as bait; recombinant expression of the same in host cells; generation of an antibody to said proteins; a method for generating transgenic plants that exhibit reduced synthesis of said cell cycle interacting proteins; identification of corresponding promoter sequences of said proteins; method for identification of activators or inhibitors of said proteins and cell division in general by establishing a read-out system interacting with either the promoter region or the protein and operating the read-out system in the presence of a compound; method of producing a therapeutic or plant effective agent containing said activator or inhibitor; a

composition containing said genes, proteins, vectors, antibodies or activators or inhibitors for use as a medicament or plant effective agent; use of the nucleotide sequences representing said proteins or promoters in marker-assisted breeding.

Invention 4: Claims 1,5-38,40 partially

As invention 1 but limited to the VB89 protein as characterized in SEQIDs 7 and 8.

3). No Search (Box III)

Claim 34 was found to be unsearchable. Claims 35-37 embrace i.a. the unknown and unsearchable activator or inhibitor of claim 34. Consequently, this claim and claims 35-37 as far as related to subject matter of claim 34 cannot be examined. Examination is thus restricted to claims 1, 5-33, 38 and 40 and claims 35-37 partially.

4). Prior Art

D1: CULIANEZ-MACIA, F.A., ET AL. : 'Arabidopsis HAL3A: identification of a novel flavoprotein which regulates plant growth and salt tolerance - unpublished' EMBL SEQUENCE DATA LIBRARY, 19 January 1997 (1997- 01-19), XP002144143 heidelberg, germany

D2: CULIANA-MACIA, F.A:, ET AL. : 'Arabidopsis thaliana HAL3 homolog gene' SWISSPROT DATABASE, 1 May 1997 (1997-05-01), XP002144144

D3: DE VEYLDER LIEVEN ET AL: 'The Arabidopsis CKs1At protein binds the cyclin-dependent kinases Cdc2aAT and Cdc2bAt.' FEBS LETTERS 1997, vol. 412, no. 3, 1997, pages 446-452, XP002047992 ISSN: 0014-5793

D4: DE NADAL EULALIA ET AL: 'The yeast halotolerance determinant Hal3p is an inhibitory subunit of the Ppz1p Ser/Thr protein phosphatase.' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 95, no. 13, 23 June 1998 (1998-06-23), pages 7357- 7362, XP002144145 June 23, 1998 ISSN: 0027-8424

D5: DE VEYLDER L ET AL: 'Identification of proteins interacting with the Arabidopsis Cdc2aAt protein.' JOURNAL OF EXPERIMENTAL BOTANY DEC.,

1997, vol. 48, no. 317, December 1997 (1997-12), pages 2113-2114, XP002067456 ISSN: 0022-0957

D6: WO 98 41642 a (VEYLDER LIEVEN DE ;VLAAMS INTERUNIV INST BIOTECH (BE); INZE DIRK () 24 September 1998 (1998-09-24)

D7: WO-a-9841642

D8: WANG H. ET AL.: 'ICK1, a cyclin-dependent protein kinase inhibitor from Arabidopsis thaliana interacts with both Cdc2a and CycD3, and its expression is duced by abscisic acid.' PLANT J 1998 AUG;15(4):501-10, XP002054969

D9: SEGERS GERDA ET AL: 'The Arabidopsis cyclin-dependent kinase gene cdc2bAt is preferentially expressed during S and G-2 phases of the cell cycle.' PLANT JOURNAL 1996, vol. 10, no. 4, 1996, pages 601-612, XP002138663 ISSN: 0960-7412

D10: WO 98 03631 a (SALK INST FOR BIOLOGICAL STUDI) 29 January 1998 (1998-01-29)

D11: WO-a-9803631

D12: CHEN, J., ET AL. : 'arabidopsis thaliana gene expression microarray - unpublished' EMBL SEQUENCE DATA LIBRARY, 9 September 1999 (1999-09-09), XP002144147 heidelberg, germany

D13: ESPINOSA-RUIZ, a., ETAL. : 'Arabidopsis thaliana AtHAL3: a flavoprotein related to salt and osmotic tolerance and plant growth' THE PLANT JOURNAL , vol. 20, no. 5, December 1999 (1999-12), pages 529-539, XP002144146

5). Priority (Box II)

If the priority is not valid, which could not be checked, D12 will become relevant.

6). Novelty, Inventive Step and Industrial Applicability (Box V)

6.1). Novelty (Art. 33 (2) PCT)

Invention 1

The sequence for LDV115, SEQ ID NO: 1 and 2 appears to be novel with regard

to the cited prior art.

Invention 4

Claim 1 relates to a DNA sequence encoding a cell cycle interacting protein or encoding an immunologically active fragment of such a protein. D1 discloses a shorter sequence of HAL3. The description of the present application states on page 72 "Except that VB89 is longer, there are no major differences with this cDNA"
Thus the subject matter of claim 1(d) lacks novelty (Art. 33 (2) PCT).
Also the follow-up claims to the vector and the host cell of claims 5-11 as well as a composition comprising the DNA sequence of claims 35 and 36 lack novelty over D1 (or inventive step claims 12-33, 35-38 and 40 see below).

Invention 1 and invention 4

Moreover claim 1 does not require that the DNA sequence must be **isolated** consequently claim 1 as presently worded embraces sequences in their natural environment.

6.2). Inventive Step (Art. 33 (3) PCT)

Invention 1 and 4

The use of yeast two-hybrid system to identify Arabidopsis thaliana proteins interacting with CDC2aAt or CDC2bAt is known from D3, D5-D7.
Thus the problem to be solved by the present application is the identification of further plant specific cell cycle interacting proteins.

Invention 1

With regard to the LDV115 gene the description teaches (page 102) that said gene encodes a protein which interacts with CDC2a but not with DCD2b and it shows a limited similarity to the S. cerevisiae WEB1 protein. Screening publicly available databases revealed the WEB1 protein from S. pombe as best

homologue due to the proline-richness of LDV115. However, proline-rich regions are not restricted to the WEB1 protein but can also be found in many structural proteins. Therefore it is concluded in the description that "LDV115 might not be a true homologue of WEB1."
Having regard to the description apparently no physiological function or activity was determined or confirmed for LDV115 in the present application. (The ability to interact with CDC2a cannot be taken as the physiological function in view of other proteins interacting with CDC2aAt (D5).)
Thus since no proven or probable physiological function is demonstrated in the present application the only technical problem underlying the present application that could be identified by the IPEA merely resides in the cloning of new sequences and provision of the proteins with no determined/confirmed function or specific and substantial utility.
This is a "minimalist" problem which is not technically meaningful. The solution is a non-inventive selection from a host of polypeptides.
Consequently, claims 1, 5-33, 35-38 and 40 of invention 1 do not meet the requirements of Art. 33 (3) PCT.

Invention 4

With regard to D1 which is considered the closest prior art document and in combination with either D3, D5-D6 or D7 the subject matter of claims 12-33, 35-38 and 40 lack an inventive step (Art. 33 (3) PCT).

6.3). Industrial Applicability (Art. 33 (4) PCT)

Invention 1

The above analysis of the description and arguments are also of importance when considering the industrial applicability.

No physiological function or activity has been determined for LDV115.
Thus the DNA sequence and the polypeptide (LDV115) encoded by said sequence can be used to assess the properties or functions of said protein and thus serve as a starting point for further research.

Art. 33(4) PCT requires that the invention can be **made or used** in order to have industrial applicability. According to Rule 5(vi) PCT the description must indicate explicitly, when it is not obvious from the description or nature of the invention, the way in which the invention is capable of exploitation in industry and the way in which it can be made or used.
Also the PCT International Preliminary Examination Guidelines, Chapter IV-4. (WIPO 1998) state that "a claimed invention shall be considered industrially applicable, if according to its nature, it can be made or used (in the technological sense) in any kind of industry".

Which impact have these requirements on nucleic acid molecules and polypeptides?
No doubt the nucleic acid molecules and polypeptides can be **made**.

Is this sufficient to have industrial applicability?
Making nucleic acid molecules and polypeptides without any purpose is technically and industrially not meaningful (like copying information).

Thus for chemical compounds such as nucleic acid molecules and polypeptides the **use** requirement of Art. 33(4) and Rule 5(vi) PCT must be fulfilled. This means that there must be a function/biological/physiological activity attributed to said specific nucleic acid molecule or polypeptide, which shows its industrial applicability or at least makes it plausible.
The mere finding that this protein interacts (how?) with CDC2aAt is generally not sufficient in view of the cited prior art.
It follows that in the present case the skilled person has to carry out research programme in order to find out how the DNA sequence or protein can be used in industry other than for research purposes.
Hence, with regard to the above, the subject matter of claims 1, 5-33, 35-38 and 40 does not meet the requirement of Art. 33(4)and Rule 5 (vi) PCT.
In view of the lack of determined biological activity/function of the polypeptides and in view of the speculative uses the industrial applicability does not appear to be plausible.

Invention 4

With regard to the function (role) of HAL3 of yeast and with regard to the sequence identity, it appears plausible that VB89 is a homologue to yeast HAL3.

7). Concluding remark with regard to invention 1

All that the invention 1 provides is a starting point for an invitation to carry out a research programme for the next years. This cannot be called a complete invention.

8). Clarity (Art. 6 PCT) (Box VIII)

Claim 1 does not specify that the identity must be over the entire length which renders the claim speculative.

Since the function of the protein at least for invention 1 was not determined it is not clear for which function the skilled person should look (test) when testing all the proteins or parts thereof which have 60% identity. Consequently, claim 1 is unclear.